VOLUME XIV AUGUST 1958 NUMBER 8

Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Friday at 12:30 P.M., from the Clinicopathological conferences and from the monthly Staff meeting.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $3.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D.C. Please notify on change of address.

Entered as second class matter November 21, 1946 at the post office at Washington, D.C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

CHLOROMYCETIN ACID SUCCINATE (SODIUM SALT)

Some Preliminary Clinical and Laboratory Observations in Infants and Children

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INTRODUCTION

Parenteral administration of antibiotics occupies a uniquely important role in pediatrics (particularly in hospitalized patients) because of the vicissitudes of the oral route of administration. When a child is extremely ill, semi-comatose or refractory to ingestion of oral medication, the desirability of parenteral administration becomes manifest. In that regard, one of the notable virtues of penicillin has been the availability of both short and long acting, well tolerated intramuscular preparations as well as an adequate intravenous form of the drug. Parenteral preparations of the broad spectrum antibiotics have fared less admirably, however. In the case of the tetracyclines, the intravenous forms have been moderately well tolerated and adequate blood levels can be maintained with a dosage of 10 mg. per kg. every six hours. However, the intramuscular preparations produce some degree of local irritation in many patients, particularly when dosages higher than 5 mg. per kg. of body weight at 12 hour intervals are employed. Intramuscular tetracyclines have to be injected deeply into the body of the gluteus muscle and care must be taken to avoid the subcutaneous and fatty layers. It should be added parenthetically that this is not always possible in the small marasmic infant whose muscle endowment is rather sparse. In addition, intramuscular preparations contain procaine and may conceivably produce occasional reactions in children with procaine hypersensitivity. Also, one must avoid the inadvertent intravenous injection of the intramuscular preparation.

Until recently, there have been two available forms of chloramphenicol for parenteral use. However, both *Chloromycetin Solution*, designed pri-

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From the Research Foundation of Children's Hospital, Washington, D. C. The Chloromycetin Acid Succinate employed in this study was generously supplied by Dr. Harry Carnes, Parke, Davis and Company, Detroit. We are indebted to Mr. Charles Tappan for his technical assistance. This article has already appeared in Antibiotics Annual (1957–1958) and is reprinted with the permission of Dr. Henry Welch.

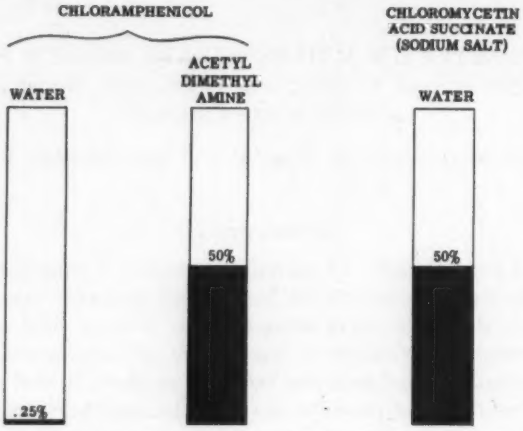

FIG. 1. Comparison between solubility of chloramphenicol and chloromycetin acid succinate.

marily for intravenous use, and *Chloromycetin Intramuscular*, a microcrystalline aqueous suspension designed for intramuscular administration, possess definitive drawbacks and are somewhat less than ideal preparations.

Recently a new form of parenteral chloramphenicol, *Chloromycetin Acid Succinate* (Sodium Salt) has been made available for clinical and pharmacological evaluation. This material is a sodium salt of the monosuccinate ester of chloramphenicol. It is highly soluble in aqueous solution (greater than 50 per cent) and hence overcomes many of the disadvantages of the present forms of intravenous and intramuscular chloramphenicol (fig. 1). Preliminary observations indicated that the sodium salt of *Chloromycetin Acid Succinate* possesses such ready solubility that one gram of material goes into solution in as little as 5 ml. of any of the crystalloid solutions, including normal saline, M/6 lactate, 5 per cent glucose in water or polyionic solutions. This is in contrast to non-esterified chloramphenicol which possesses neither acidic nor basic groups capable of forming salts soluble in aqueous media and hence requires an organic solvent to get it into solution.

The present study summarizes some of the pharmacological properties as well as the results of a preliminary clinical trial of *Chloromycetin Acid Succinate* in the pediatric age group.

METHODS AND MATERIALS

In order to calibrate optimal dosage in the pediatric age group, *Chloromycetin Acid Succinate* was administered to a series of infants and children both intravenously and intramuscularly in varying single and multiple doses related to body weight.

Spinal fluid levels and serum levels were obtained concomitantly in order to determine the degree of diffusion across the blood-brain barrier both in children with normal meninges and in those with acute bacterial meningitis.

Chloramphenicol bioassays were performed by the cup plate method employing a spore suspension of *B. mycoides* as the test organism. With this method, the minimum detectable concentration was 2 mcg. per ml.

Thirty-nine infants and children with moderate to severe bacterial infections including *H. influenzae* meningitis, *Staphylococcus aureus* septicemia, Rocky Mountain spotted fever, acute laryngotracheobronchitis, bacterial pneumonia, salmonellosis, shigellosis, and pathogenic *E. coli* gastroenteritis were treated with *Chloromycetin Acid Succinate* administered parenterally. Forty-one additional pediatric patients were also included in the study for evaluation of side effects and toxicity. Approximately one half of the patients in the present series received *Chloromycetin Acid Succinate* intravenously initially in a dosage of 25 mg. per kg. of body weight every six hours for one to three days (the reconstituted drug in a concentration of 200 mg. per ml. of water being added directly to the drip meter of the intravenous set); following this, the intramuscular route was employed in a dosage of 50 mg. per kg. every 12 hours. The remaining 50 per cent of the patients received only intramuscular *Chloromycetin Acid Succinate* throughout the entire course of therapy. The intramuscular form was prepared by reconstituting a vial of 0.5 Gm. of *Chloromycetin Acid Succinate* with 2.5 ml. of water or normal saline and injecting it without further dilution. Parenteral therapy was usually maintained for 5 to 13 days depending on the type and severity of the infection. Oral chloramphenicol (Chloromycetin palmitate) was employed in only 5 patients in the present series and this was given only during the convalescent phase of the illness. The intensive emphasis on the parenteral route in this group of patients was predicated primarily on the desire to give *Chloromycetin Acid Succinate* a proper evaluation both for clinical efficacy and tolerance.

Attention was directed toward the possible occurrence of side reactions and toxic effects in all 80 patients. This included careful observations for evidence of local tissue irritation at the site of intramuscular injection, thrombophlebitis following intravenous administration, gastrointestinal disturbances, and any evidence of depression of the hematopoietic system elements.

RESULTS

I. Laboratory Observations

a) *Intramuscular Chloromycetin Acid Succinate*

In order to determine the optimal dose and frequency of administration of *Chloromycetin Acid Succinate* intramuscularly, four children varying in

age from 5 to 8 years and ranging in weight from 20 to 30 kg. were given a dosage of 50 mg. per kg. at 12 hour intervals for two doses. Serum levels were determined after 2, 6, 12, 14, 18 and 24 hours. Thus, the first three assays were obtained after the first dose while the 14, 18 and 24 hour levels were performed 2, 6 and 12 hours after the second dose. The levels were therefore those which might be found during ordinary therapeutic administration of the drug.

The resulting chloramphenicol assays are averaged and presented in figure 2. There were individual variations from one child to another but the average values were sufficiently representative to establish a dosage regime.

As may be seen (fig. 2), an average peak concentration of 14.1 mcg. per ml. was achieved within two hours after the first dose and a gradual tapering off occurred thereafter. At the end of 12 hours, an average value of 4.4 mcg. per ml. was obtained. Following the next dose of *Chloromycetin Acid Succinate*, a second peak level of 19.5 mcg. per ml. was attained two hours later; this was substantially higher than the first peak level (14.1 mcg. per ml.). Again there occurred a gradual drop in serum concentrations during the next 12 hours; however even at this point an average serum level of 7.1 mcg. per ml. was still observed.

From these data, it is clear that good therapeutic levels of chloramphenicol could be maintained throughout an entire 24 hour period by

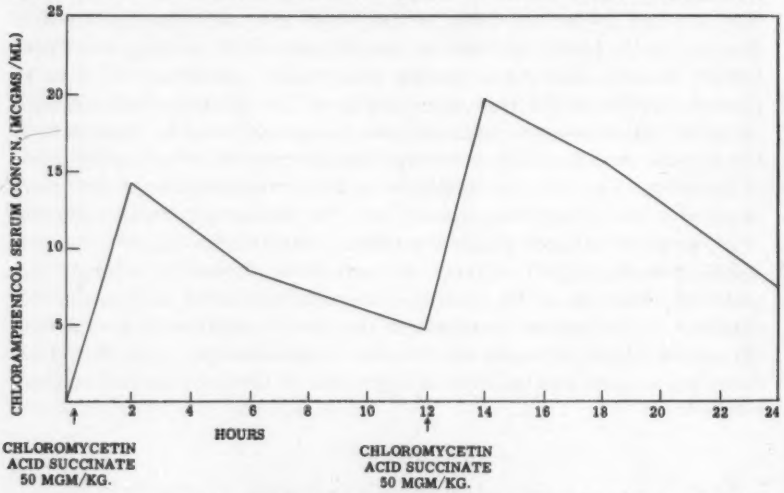

FIG. 2. Average chloramphenicol blood levels (mcgms/ml.) obtained after I.M. administration of chloromycetin acid succinate in a dose of 50 mgm/kgm every 12 hrs. for two doses.

employing a dosage of 50 mg. per kg. of *Chloromycetin Acid Succinate* intramuscularly at 12 hour intervals. Of ancillary interest were the staircase increments observed in serum concentrations when a dosage interval of 12 hours was used.

In order to compare serum chloramphenicol levels achieved with equal doses of *Chloromycetin Acid Succinate* and *Chloromycetin Intramuscular*, the latter preparation was given to a group of four children in a single intramuscular dose of 50 mg. per kg. Serum chloramphenicol levels were then obtained at 3, 6, 12, 18 and 24 hours. The resulting levels were compared with a second group of four children who had received a single intramuscular dose of 50 mg. per kg. of *Chloromycetin Acid Succinate*. Each group of children was comparable in age and weight.

The resulting average serum levels are compared in figure 3. As will be noted, with *Chloromycetin Acid Succinate*, peak levels averaging 18.3 mcg. per ml. were obtained after two hours followed by a relatively gradual tapering off, so that after 12 hours the average concentration was 4.3 mcg. per ml., and after 24 hours had slowly declined to 2.7 mcg. per ml. By way of contrast, the average serum levels achieved with *Chloromycetin Intramuscular* were considerably less; a peak value of 7.9 mcg. per ml. was attained only after six hours followed by a very gradual drop during the next 18 hours. The chief difference in serum concentrations between the two preparations was apparent in the first 12 hours, with *Chloromycetin Acid Succinate* showing off to a substantially greater advantage both in

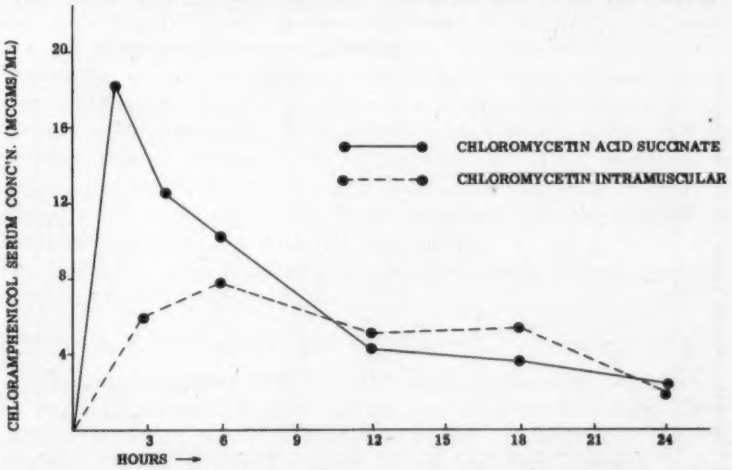

FIG. 3. Comparison between average blood levels obtained after a single 50 mgm/kgm dose of chloromycetin acid succinate and chloromycetin intramuscular.

regard to the height of the levels as well as the rapidity with which they were attained.

It is apparent from these data that *Chloromycetin Acid Succinate* has two virtues which redound to the success of an intramuscular preparation: 1) rapid absorption with resulting production of high serum levels quickly; and 2) persisting therapeutic concentrations over a relatively prolonged period, a property which signifies repository qualities and may thus reduce the frequency of injections.

b) *Intravenous Chloromycetin Acid Succinate*

In the pediatric age group, where severe bacterial infections often must be treated extremely vigorously in order to influence the outcome, a practical intravenous preparation of an antibiotic is highly desirable.

In order to calibrate optimal dosage requirements for *Chloromycetin Acid Succinate* intravenously, a group of seven children ranging in age from 5 to 7 years and varying in weight from 20 to 25 kg. was given a single intravenous dose of 20 mg. per kg.; serum levels were then obtained after one, two, four, six and eight hours.

The resulting average values are presented in figure 4. As may be seen, a peak level of 8.5 mcg. per ml. was attained in one hour followed by a gradual tapering off. A minimal therapeutic level of 5.3 mcg. per ml. was present at four hours while suboptimal concentrations of 3.7 and 3.9 mcg. per ml. were obtained at six and eight hours respectively.

Since these levels were somewhat disappointing, the dose was raised to

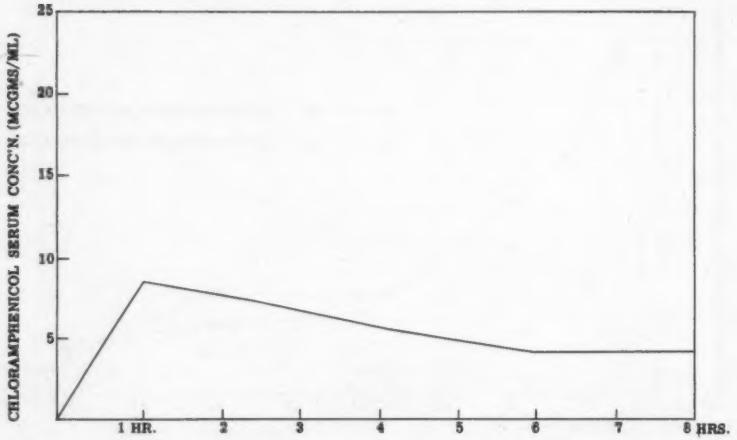

FIG. 4. Average chloramphenicol blood levels (mcgms/ml.) obtained after a single intravenous dose of chloromycetin acid succinate (20 mgm/kgm).

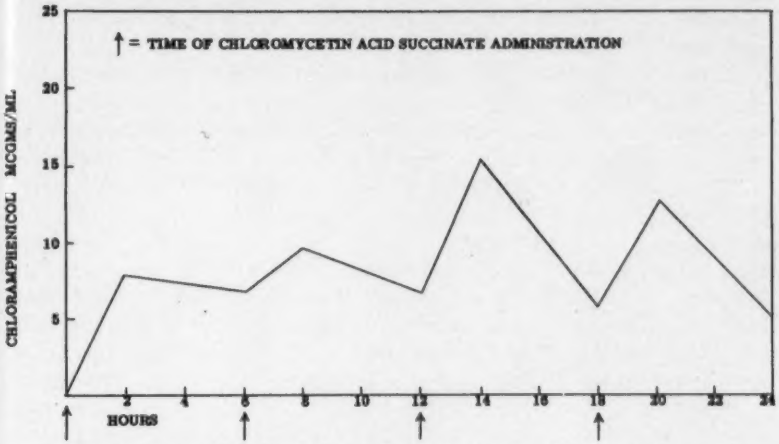

FIG. 5. Average chloramphenicol blood levels (mcgms/ml.) obtained after I.V. administration of chloromycetin acid succinate in a dose of 25 mgm/kgm every 6 hrs. for 4 doses.

25 mg. per kg. and given every six hours intravenously in order to simulate actual clinical use of the drug; serum levels were obtained two and six hours after each of the four doses. The resulting average serum concentrations are presented in figure 5. As will be observed, the average serum levels were moderately well maintained during the entire 24 hour period when this dosage schedule was employed.

COMMENT: By way of summary, *Chloromycetin Acid Succinate* may be given either intramuscularly or intravenously with the production of adequate therapeutic serum levels. With both modalities of administration, a total daily dose of 100 mg. per kg. is recommended. If the intramuscular route is employed, *Chloromycetin Acid Succinate* should be given every 12 hours in a dose of 50 mg. per kg.; if given intravenously, the drug may be given every six hours in a dose of 25 mg. per kg.

It should be noted that these dosage recommendations are pertinent only to the pediatric age group.

c) *Diffusion of Chloromycetin Acid Succinate into the Cerebrospinal Fluid*

1) IN CHILDREN WITH NORMAL MENINGES. In an effort to determine the degree of diffusion of *Chloromycetin Acid Succinate* across the blood-brain barrier, serum and spinal fluid chloramphenicol levels were obtained simultaneously in a group of four infants and children with normal meninges who were receiving the drug either intramuscularly or intra-

venously in a total daily dose of 100 mg. per kg. The resulting levels are presented in Table I.

As may be seen in Table I, the concentration of chloramphenicol in the spinal fluid averaged 46 per cent of the coexisting serum level. From these data, one can conclude that *Chloromycetin Acid Succinate* diffuses readily across the hematocephalic barrier even in children with normal meninges.

2) In Children with Inflamed Meninges. Ordinarily one would expect some increase in diffusion across the blood-brain barrier in instances of inflamed meninges. To assess this point, simultaneous serum and spinal fluid chloramphenicol assays were performed on 10 children with *H. influenzae* meningitis who were being treated with *Chloromycetin Acid Succinate* parenterally in a total daily dose ranging between 70 and 200 mg. per kg. Specimens were obtained from one to seven days after initiation of therapy. The results are presented in Table II.

As will be noted in Table II, the average cerebrospinal fluid level was 40 per cent of the coexisting serum concentration. Thus, there appeared to be no significant difference between the diffusion of *Chloromycetin Acid Succinate* across inflamed or normal meninges. The main point to emphasize is that *Chloromycetin Acid Succinate* diffuses across the blood-brain barrier readily and predictably, producing an excellent concentra-

TABLE I

Chloramphenicol Levels (mcg. per ml.)

Patient	Serum	Spinal Fluid	Spinal Fluid/Serum Ratio
G. S.	56.0	18.0	32%
C. L.	10.0	5.0	50%
J. C.	10.2	6.7	66%
P. S.	27.0	10.0	37%
			Average 46%

TABLE II

Chloramphenicol Levels (mcg. per ml.)

Patient	Day After Rx Started	Serum	Spinal Fluid	Spinal Fluid/Serum Ratio
1	1	52.0	19.0	37%
1	1½	40.0	16.0	40%
1	3	40.0	16.0	40%
1	7	8.8	3.9	44%
2	1½	18.0	7.8	43%
2	4	4.2	2.4	57%
2	6	10.0	2.0	20%
				Average 40%

tion in the spinal fluid. It is needless to belabor the importance of this fact in the treatment of pyogenic meningitis.

d) *Hematopoietic Depressant Effect of Chloromycetin Acid Succinate*

Repeat hemograms were obtained on all 80 infants and children while receiving *Chloromycetin Acid Succinate* to determine whether any myelotoxic effect occurred.

One patient, a 6 month old infant, had an admission white cell count of 20,000 with 31 per cent neutrophils. Within three days after initiation of *Chloromycetin Acid Succinate*, the white cell count had dropped to 10,400 with 6 per cent neutrophils. Because of the resulting neutropenia, the drug was discontinued and within two days, the neutrophils had risen to 17 per cent.

A second patient, a 10 month old infant, developed a mild leukopenia of 5,000 white cells with 20 per cent polymorphonuclear leukocytes within five days after *Chloromycetin Acid Succinate* was started. After discontinuation of the drug, the white cell count and differential returned to normal within five days.

A third patient, a 2 year old child, showed 11,700 white cells with 70 per cent neutrophils on admission. Within five days after initiation of *Chloromycetin Acid Succinate* therapy, the white cell count was 4,200 with 5 per cent neutrophils, and two days later dropped still further to 3,500 with 2 per cent neutrophils. Chloramphenicol was discontinued and daily hemograms obtained thereafter showed a gradual return to normal. Five days after the drug was stopped, the white cell count had risen to 8,100 with a normal differential. No significant depression of the hematopoietic system was observed in the 77 other patients.

II. Clinical Evaluation of Chloromycetin Acid Succinate

At the present time, we are in the process of evaluating *Chloromycetin Acid Succinate* clinically. Thus far a group of 39 children ranging in age from 6 days to 12 years have been treated for a variety of bacterial infections.

The diseases treated with a clinical and laboratory response designated as good, fair or poor are presented in Table III.

With the group of bacterial infections referred to in Table III, one might make the general statement that the response to *Chloromycetin Acid Succinate* appeared to approximate the results one would anticipate with any of the other forms of chloramphenicol hitherto available, although it would be difficult to quantitate this clinical impression. In any event, *Chloromycetin Acid Succinate* had the virtue of simplicity, convenience and ease of administration in the present series.

TABLE III
Clinical Evaluation of Chloromycetin Acid Succinate

Type of Infections	No. of Cases	Response		
		Good	Fair	Poor
Upper Respiratory Infections	3	3		
Acute Laryngotracheobronchitis	3	3		
Bronchopneumonia	4	4		
H. influenzae meningitis	2	2		
Rocky Mountain spotted fever	1	1		
Shigella dysentery	14	14		
Salmonella enteritis	6	2	2	2
Pathogenic *E. coli* gastroenteritis	4	4		
Staphylococcus aureus septicemia	2	2		
	—	—	–	–
	39	35	2	2

For the purposes of illustration, brief resumes of representative cases are summarized as follows:

Bacterial Pneumonia (Fig. 6)

L. Y., a 5 year old colored boy, was admitted to Children's Hospital on August 12, 1957 with a two day history of fever, headache and lethargy. There were diminished breath sounds over both lung fields posteriorly. Temperature was 104° F. X-ray of the chest showed an area of infiltration in the right upper lobe. The white cell count on admission was 44,400 with 87 per cent neutrophils.

On the day of admission, *Chloromycetin Acid Succinate* was started in a dosage of 900 mg. every 12 hours intramuscularly (total 100 mg. per kg. per day). Within 48 hours after initiation of therapy, the temperature returned to normal and the child appeared considerably improved clinically.

Three days after admission, x-ray of the chest revealed a moderate degree of resolution of the pneumonic process. At this time, the white cell count had dropped to 12,700 with 56 per cent polymorphonuclear leukocytes. On August 22, a follow-up chest x-ray was entirely normal.

Therapy was discontinued on the tenth day after an uneventful course.

COMMENT: Although no specific causative organism was isolated in this patient, it was apparent from the white cell count (44,400 with 87 per cent neutrophils) and the x-ray evidence of lobar consolidation that one was dealing with a bacterial pneumonia, probably due to *Diplococcus pneumoniae*. The response to intramuscular *Chloromycetin Acid Succinate* was quite adequate and compared favorably with those cases of bacterial pneumonia previously managed with oral chloramphenicol in this hospital[1].

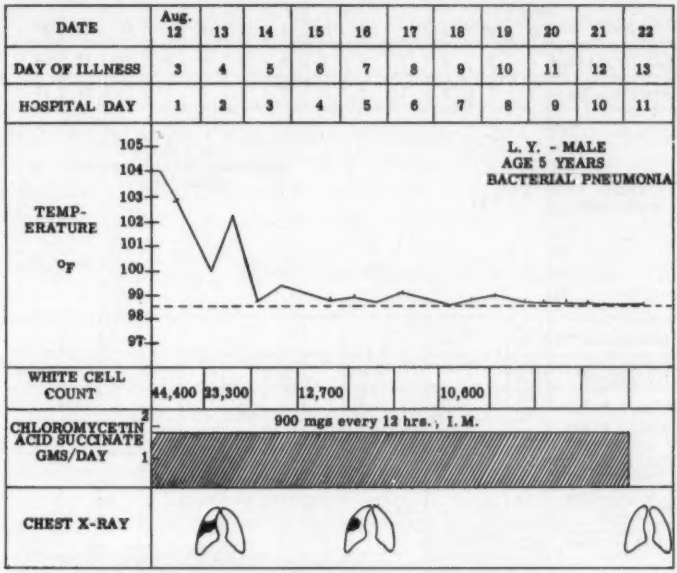

FIGURE 6.

H. Influenzae *Meningitis* (*Fig. 7*)

U. J., a 3 year old colored boy, was admitted to Children's Hospital on August 8, 1957 with a history of fever and anorexia of two days' duration. He was acutely ill and lethargic and there was moderate nuchal rigidity. Temperature was 104° F.

Laboratory examinations showed a white cell count of 13,200 with 68 per cent neutrophils. The cerebrospinal fluid contained 755 white cells per cu. mm. with 71 per cent neutrophils and 29 per cent lymphocytes; protein was 31 mg. per 100 ml. and sugar was 54 mg. per 100 ml. Spinal fluid culture grew out *Hemophilus influenzae*, type B. Blood culture on admission also grew out *H. influenzae*, type B.

Within two hours after admission, *Chloromycetin Acid Succinate* was started intravenously in a dosage of 335 mg. every six hours for three doses and then 700 mg. every six hours for the next two days. Thereafter, the drug was administered intramuscularly in a dosage of 550 mg. every 12 hours for four days at which time the dosage was raised to 750 mg. twice a day.

Within 24 hours after initiation of therapy, the temperature dropped precipitously to normal and the child remained substantially afebrile during the remainder of his hospital course. Concomitantly, the patient showed excellent improvement clinically. Spinal fluid and blood cultures obtained two days after treatment was started were negative. The spinal fluid cell count decreased after the first 48 hours of therapy and a shift to lymphocytic predominance was observed during the first week.

Chloromycetin Acid Succinate therapy was maintained for 13 days at which time

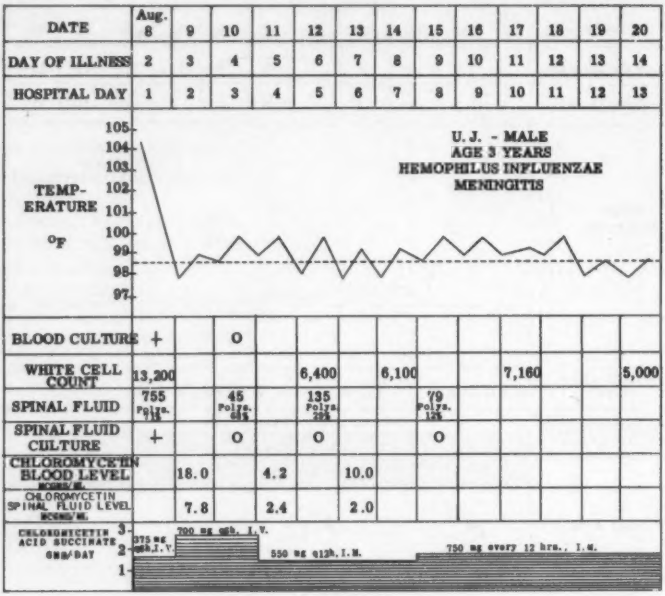

FIGURE 7.

the child was discharged as completely recovered with no evidence of neurological sequellae.

COMMENT: The response to *Chloromycetin Acid Succinate* therapy in this patient was impressive since no other drugs were employed. In spite of intensive therapy for 13 days, the child tolerated the medication extremely well.

A second case of *H. influenzae* meningitis was similarly managed with *Chloromycetin Acid Succinate* alone and responded in much the same salutary fashion.

It is our belief that *H. influenzae* meningitis can be treated successfully with *Chloromycetin Acid Succinate* alone. One would recommend three or four days of intravenous therapy followed by intramuscular treatment for another 10 days. Using parenteral *Chloromycetin Acid Succinate* exclusively for the entire course of therapy would, in our minds, preclude the possibility of relapses which may ensue when therapy is switched to the oral route prematurely.

DISCUSSION

From the previously described clinical and laboratory observations, one would be prone to regard *Chloromycetin Acid Succinate* as a distinct advance

in parenteral chloramphenicol therapy. The question logically arises whether its advantages are such that it distinctly overshadows the hitherto available parenteral forms of chloramphenicol and perhaps even renders the latter obsolete. It would be our thesis that such might be the case.

Tables IV and V present a concise comparison between the previously available parenteral preparations of chloramphenicol and *Chloromycetin Acid Succinate*. It would be well to review and summarize the advantages and disadvantages of each of these forms of the drug.

1) *Comparison of Intravenous Forms of Chloramphenicol*

a) *Chloromycetin Solution*

This preparation is intended primarily for intravenous use and is supplied in 2 ml. size ampoules containing 0.5 Gm. of chloramphenicol in a 50 per cent aqueous solution of acetyl dimethylamine, an organic solvent. The resulting solution must then be very carefully diluted with approximately 150 ml. of crystalloid solutions such as normal saline or 5 per cent glucose in water for each 0.5 Gm. of chloromycetin solution. The multiple list of precautions one must adhere to in preparing *Chloromycetin Solution* for clinical use are enumerated as follows:

1. *Chloromycetin Solution* should be warmed to body temperature and shaken well.
2. The solution must be withdrawn from the ampoule with a dry syringe

TABLE IV

Comparison of Intravenous Forms of Chloramphenicol

Drug Form	Solvent	Diluent	Individual Dose	Dosage Interval	Comment
Chloromycetin Solution	Acetyl Dimethylamine	N. saline 5% glucose in water	20 mgm/kgm	Every 6 hours	Many precautions required in preparation. Precipitates very readily. Large volume of fluid required as diluent.
Chloromycetin Acid Succinate (Sodium Salt)	N. saline distilled water	N. saline 5% glucose in water polyionic solutions	25 mgm/kgm	Every 6 hours	Very soluble in aqueous solution. Easily prepared for IV use. Does not precipitate. Only small volume of diluent required.

TABLE V

Comparison of Intramuscular Forms of Chloramphenicol

Drug Form	Solvent	Individual Dose	Dosage Interval	Comment
Chloromycetin Solution	Acetyl Dimethylamine	25 mgm/kgm	Every 6 hours	Moderate pain at site of injection. Give every 6 hours to maintain blood levels. Inject deep IM to prevent tissue necrosis. Can be used either IM or IV.
Chloromycetin Intramuscular	N. saline distilled water	100 mgm/kgm	Every 24 hours in infants, every 12 hours in older children	Easily suspended in aqueous solution. Repository form of chloramphenicol producing prolonged blood levels lasting 24 hours or longer. Local tissue irritation at site of injection in approximately 25% of cases. Tissue necrosis and sloughing may occasionally occur after intensive prolonged therapy particularly in infants. Can only be given IM. Blood concentrations not consistent with dose given particularly in older children and adults.
Chloromycetin Acid Succinate	N. saline distilled water	50 mgm/kgm	Every 12 hours	Goes into aqueous solution readily. Well tolerated IM with minimal pain at site of injection. No sloughing or necrosis. Rapid absorption from injection site. Can be given IM or IV. Blood levels more predictable with a given dose.

and then the needle changed to eliminate the possibility of a droplet coming in contact with the surface of the diluent.

3. *Chloromycetin Solution* must then be rapidly discharged with the tip of the needle *beneath* the surface of the diluent (between 100 and 250 ml. of normal saline or 5 per cent glucose in water). Extreme care must be taken to add *Chloromycetin Solution* to the selected diluent rather than the reverse since the latter would in all probability result in precipitation of the material and it would have to be discarded.

In spite of the aforementioned precautions, not uncommonly crystallization does occur even in the most experienced hands. This factor has reduced to some extent the practicality of *Chloromycetin Solution* in the average hospital.

Another drawback to this preparation is the fact that a large volume of fluid must be given as a diluent, a not too desirable feature in small infants where overhydration can be readily achieved with preciously little effort.

b) *Chloromycetin Acid Succinate* (*Sodium Salt*)

In sharp contrast, *Chloromycetin Acid Succinate* is highly soluble, and is easily prepared as an aqueous solution. For intravenous use, it requires no special precautions and will not precipitate under any circumstances no matter how impoverished one's technique may be. Only a small volume of diluent is necessary, a distinct advantage in the pediatric age group. The concentrated aqueous preparation can be added directly to the drip meter or injected slowly into the tubing of an intravenous set.

To a first approximation, the dose and frequency of administration of both *Chloromycetin Solution* and *Chloromycetin Acid Succinate* are similar[2]. A regime of 25 mg. per kg. every six hours may be employed with each.

Little if any thrombophlebitis was encountered with *Chloromycetin Acid Succinate* in the present series in spite of the fact that many of the children received 8 to 12 doses of relatively concentrated material intravenously over the course of two to three days. In addition, little tissue irritation was encountered when the drug was inadvertently deposited extravascularly.

2) *Comparison of Intramuscular Forms of Chloramphenicol*

a) *Chloromycetin Intramuscular*

As will be noted in Table V, *Chloromycetin Intramuscular*, a fine microcrystalline powder, can be suspended in either normal saline or distilled water and may be given as a single daily dose of 100 mg. per kg. in infants, with production of prolonged blood levels lasting 24 hours or longer in therapeutic concentrations. However, blood concentrations in older children and adults may be quite low with this dosage and hence, one would recommend that it be given every 12 hours (see figure 3). With *Chloromycetin*

Intramuscular, local induration and tenderness appear in approximately 25 per cent of pediatric cases particularly after intensive and prolonged therapy. Rarely, sloughing of the buttocks may occur especially in small infants. We have seen two such cases at Children's Hospital. During the past six years, we have used *Chloromycetin Intramuscular* in over 300 hospitalized children with moderate to severe infections and the results have been generally satisfactory. As previously noted however, the two chief undesirable features were 1) the degree of local tissue irritation after prolonged therapy and 2) the relatively unsatisfactory blood levels attained in older children and adults. It might also be added parenthetically that this form of chloramphenicol can only be given intramuscularly.

b) *Chloromycetin Solution*

Another preparation which can be given intramuscularly is *Chloromycetin Solution* which has been previously described as an intravenous form (see Table IV). When 0.5 Gm. of material is dissolved in 2 ml. acetyl dimethylamine, it may be given undiluted deep intramuscularly in a dosage of 25 mg. per kg. every six hours. Adequate blood levels may be achieved with this dosage regimen. Disadvantages of this form include the fact that 1) there is a moderate amount of pain at the site of injection, 2) it has to be given deeply intramuscularly to prevent tissue necrosis and 3) the drug must be given every six hours to maintain blood levels, which makes it a less adequate repository preparation than *Chloromycetin Intramuscular* or *Chloromycetin Acid Succinate*.

c) *Chloromycetin Acid Succinate*

As an intramuscular preparation, *Chloromycetin Acid Succinate* (Sodium Salt) neutralizes the objections to both aforementioned preparations. As previously noted, it goes into aqueous solution rapidly and is very readily tolerated with only a minimal amount of pain at the site of injection. Parenthetically, it might be mentioned that this is accomplished without the incorporation of procaine, hence precluding the possibility of reactions due to procaine hypersensitivity. No induration, tenderness or sloughing occurred in the present series in spite of intensive use of the drug intramuscularly for intervals as long as 10 days. Three of the older children received as much as 1.8 to 2.3 Gm. every 12 hours for seven consecutive days without any discernible local reactions. The ester was rapidly absorbed from the injection site, producing blood levels which were, to a first approximation, predictable with a given dose and were considerably higher than those achieved with the microcrystalline suspension of chloramphenicol. *Chloromycetin Acid Succinate* also possesses some intermediate repository qualities in that a dosage of 50 mg. per kg. every 12 hours produces thera-

peutic blood concentrations during an entire 24 hour period. An additional virtue of this preparation is the fact that it can serve equally well both as an intravenous and an intramuscular form endowing it with a greater versatility than any of the presently available parenteral forms of chloramphenicol. It might be added that the inadvertent intravenous injection of the drug while giving it intramuscularly carries with it no untoward effects. Where parenteral chloramphenicol is being used, it substantially simplifies the management of a given case both for the nursing and house staffs to have the same preparation serve a dual role for both intravenous and intramuscular use. In view of the ease and simplicity of its use, *Chloromycetin Acid Succinate* makes less compelling the need to switch expeditiously from parenteral to oral administration of chloramphenicol. In fact, one would be inclined to continue *Chloromycetin Acid Succinate* parenterally throughout *the entire course* of treatment and not invoke oral administration at all in instances of severe infections such as bacterial meningitis, sepsis, etc. This would be particularly pertinent in infants.

Briefly then, *Chloromycetin Acid Succinate* possesses definitive advantages over the other parenteral preparations both for intravenous and intramuscular use and should become the preparation of choice in the future.

SUMMARY

1. *Chloromycetin Acid Succinate* (Sodium Salt), because of its high solubility in aqueous solution, possesses definitive advantages over other parenteral forms of chloramphenicol hitherto available. It is well tolerated both intravenously and intramuscularly.

2. Absorption studies indicate that good therapeutic serum levels can be achieved and maintained when a dosage of 100 mg. per kg. per day is administered parenterally. For intramuscular use, a 12 hour divided dosage schedule, and for intravenous use, a 6 hour divided dosage schedule are recommended in the pediatric age group.

3. Toxicity studies on 80 infants and children who received *Chloromycetin Acid Succinate* were substantially negative except for transitory leukopenia and/or neutropenia in 3 patients.

4. Thirty-nine infants and children with moderate to severe bacterial infections including *H. influenzae* meningitis, *Staphylococcus aureus* septicemia, Rocky Mountain spotted fever, acute laryngotracheobronchitis, bacterial pneumonia, salmonellosis, shigellosis and pathogenic *E. coli* gastroenteritis were treated with *Chloromycetin Acid Succinate* parenterally. The response to therapy appeared to approximate the results one would anticipate with any of the other forms of chloramphenicol hitherto available.

5. *Chloromycetin Acid Succinate* has the virtue of simplicity and ease of administration and should become the preferential parenteral form of chloramphenicol in the future.

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TREATMENT OF ACUTE LEUKEMIA IN CHILDREN

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An appreciable increase in the survival time of the modern-day patient with leukemia has been brought about by the use of the antileukemic drugs, the antibiotics, and the steroids in the management of this disease.

Figure 1 depicts the average duration of life, after the diagnosis was made, in 127 children treated at Children's Hospital during a 20 year period. The period 1938–1947 shows a survival time of 16 weeks for the 63 patients observed. Treatment of these patients consisted primarily of blood transfusions and drugs other than the antifolic acid drugs and the antibiotics. In the succeeding years, a slow but steady and significant increase in longevity is observed. From June 1954 to June 1955 the average duration of survival of three patients was 15 weeks. Two of the three who died during this period were patients with acute myelogenous leukemia. One patient lived only one week, and the other two months after the diagnosis was made. This accounts for the sudden decrease in average length of survival time. At present there are six patients with acute lymphocytic leukemia under treatment at Children's Hospital. One of these is a 9 year old white boy who has been under treatment for three and a half years. During this time he has had several periods of remission and relapse. At present he is in relapse and is receiving 6-mercaptopurine, amethopterin and steroids.

Chemotherapeutic Agents

The two general classes of chemotherapeutic agents of value in the treatment of lymphocytic and myelocytic leukemia are the antimetabolites and the steroids.

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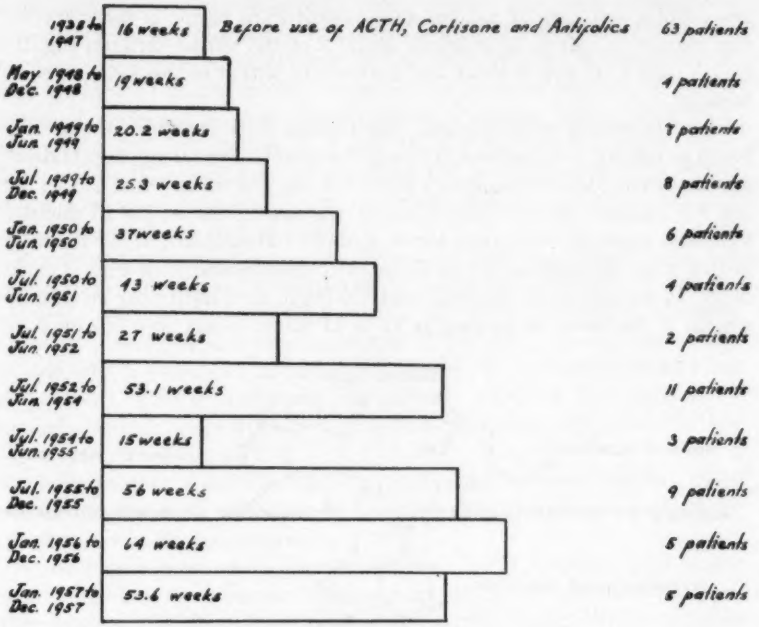

FIGURE 1.

Antimetabolites. The antimetabolites may be divided into three groups: the antagonists of folic acid, the antagonists of purines, and the azaserine group.

The folic acid antagonists (antifols) are all derivatives of 4-amino-pteroylglutamic acid. They have been obtained by substitution of an hydroxy group by an amino group in position 4. They were first used as antileukemic drugs in 1948. The two compounds of the group in common use are aminopterin (4-aminopteroylglutamic acid) and amethopterin (4-aminoazomethylpteroylglutamic acid).

The antifols have been shown to be inhibitors of certain bacterial and protozoal species, of embryonic cells, of tissue cultures, of lymphatic tissue and of bone marrow. Folic acid (pteroyl-glutamic acid or P.G.A.) and its active form, citrovorum factor (C.F.), are necessary for growth and maturation of normal erythroid and myeloid tissue of the marrow and they are even more necessary for the growth of the cells of some forms of acute leukemia. The antifols inhibit bacterial and cellular growth by entering into the cellular enzyme system which requires the presence of P.G.A. and are believed to prevent the conversion of P.G.A. into C.F. In the course of

the cellular synthesis of nucleic acids, citrovorum factor is necessary for the transfer of carbon in positions 2 and 8 of the purine skeleton (fig. 2). P.G.A. and C.F. can prevent and reverse the action of the 4-amino compounds.

In acute lymphocytic leukemia, the average daily oral dose of the antifols is as follows: aminopterin, 0.25 mg. for infants and 1.0 mg. for children; amethopterin (Methotrexate®) 1.25 to 2.5 mg. for infants and 2.5 to 5.0 mg. for children. These drugs may be detected in the serum 15 minutes following ingestion, with peak levels of about 100 micrograms per milliliter lasting from 30 minutes to two hours, with disappearance in from 2 to 12 hours. In patients with impaired renal function, significant drug levels may remain in the blood for as long as 24 to 48 hours. It has been our practice

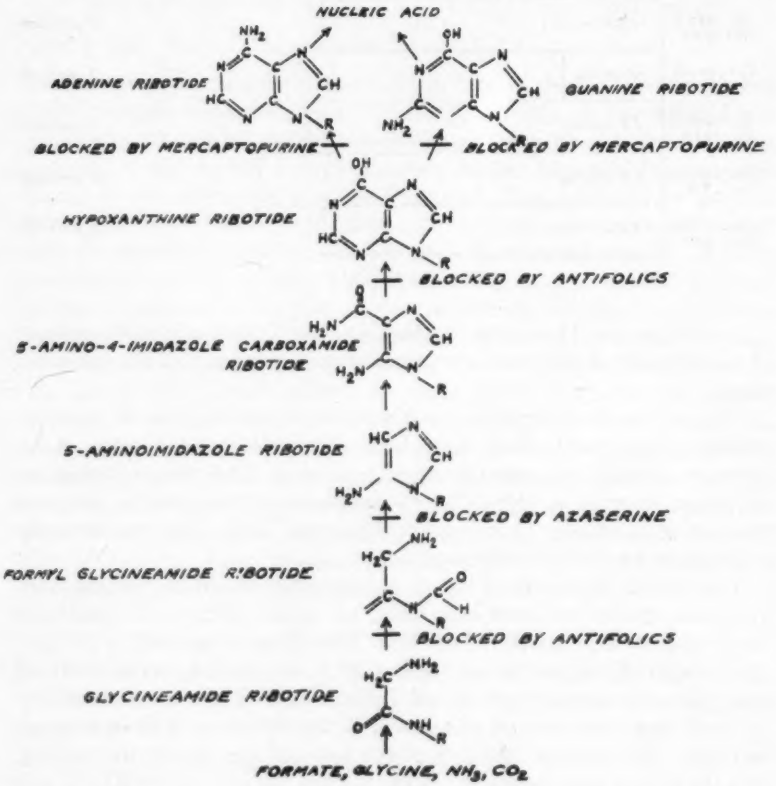

FIGURE 2.

to administer these drugs once daily. Some workers give them in fractional doses, every six to eight hours. When the average dosage is employed, the beneficial effects are rarely achieved in less than 16 days of treatment. If there are signs of improvement, treatment can be continued from a period of several weeks up to when either toxicity or relapse occurs. If there is evidence of toxicity, treatment should be discontinued for a few days. Toxic manifestations include ulceration of the mucous membranes of the mouth and gastrointestinal tract, diarrhea, loss of appetite, purpura, visceral hemorrhages and alopecia.

Remissions, when they occur, are of variable duration, ranging from one month to seven years, with an average of about eight months. In our patients the average duration of remission has been 59 days. A complete remission was obtained in approximately 30 per cent, a partial one in approximately 20 per cent and little or no benefit was noted in the remaining 50 per cent. During remission, our patients are kept on maintenance dosage, although some workers discontinue treatment once remission has been achieved.

A large number of other antagonists of folic acid have been studied. Since they are highly toxic, and have an unsatisfactory therapeutic index, they are not used in clinical practice.

Another antimetabolite, 6-mercaptopurine (6-MP, Purinethal®), was demonstrated to be a purine antagonist in studies of *Lactobacillus casei*. This compound is effective experimentally in inhibiting growth of sarcoma 180 in mice, and certain solid tumors and tissue cultures, and in preventing normal fetal and embryonic development. It appears to interfere with the metabolic synthesis of the nucleic acids of the cells by blocking the incorporation of hypoxanthines into the polynucleotides (fig. 2). Its toxic and antileukemic effects cannot be prevented nor reversed by simple purines.

Remissions may be achieved with 6-MP in some patients who have failed to benefit from, or have developed resistance to, the antifols and steroids. Remissions induced by 6-MP have been obtained in approximately 50 per cent of patients. The daily dose is 2.5 mg. per kg. of body weight, by mouth. Some physicians prefer to start the treatment with higher doses, namely 8.2 mg. per kg. of body weight, and continue this dose for about 10 days in order to achieve a more prompt and active response. The patients in our clinic, ranging from 4 to 8 years of age, receive 25 to 50 mg. per day according to their clinical condition and bone marrow and peripheral blood findings.

The action of 6-MP is slower than that of the antifolics, usually requiring three to eight weeks before beneficial effects are noted. The drug remains in the blood stream from four to six days. We administer 6-MP daily during

both relapse and remission. Some prefer to administer the drug twice a week or every 72 hours during remission.

The toxic manifestations of 6-MP are noted only occasionally and include ulcerations of the buccal mucosa, nausea and gastrointestinal disturbances. The drug may markedly depress the leukocyte count. When this happens, the level of 500 cells per cu. mm. is a definite indication for the withdrawal of the drug.

Two analogues of 6-MP, thioguanine and 6-chloropurine, are still being studied.

A third type of antimetabolite is azaserine, otherwise known as *o*-diazoacetylserine. It is an antibiotic isolated from a species of Streptomyces and is effective against several species of bacteria, the Rickettsia of epidemic typhus, sarcoma 180 and leukemia cells. It interferes with the synthesis of the nucleic acids and operates by inhibiting the conversion of formylglycineamide ribotide into 5-amino imidazole ribotide (fig. 2). This action can be reversed by glutamine.

On a dosage of 8 to 10 mg. per kg. of body weight per day, azaserine may cause moderate and temporary remissions. Within 5 to 20 days after starting treatment, redness of the tongue, ulceration of the buccal mucosa, nausea, vomiting, anorexia, electrolyte disturbances and jaundice may be noted. This drug is never used alone in the therapy of leukemia because of its only moderate effectiveness and relatively high toxicity.

In order to overcome the problem of the development of drug resistance, combinations of various antileukemic drugs have been investigated and some evidence of synergism has been noted. The sequential blocking of a single enzyme pathway at several levels by two or more compounds has been postulated and has been proven to reduce the synthesis of nucleic acid considerably more than if only one compound is used. To obtain this effect, azaserine is used in combination with 6-MP in a reduced dosage, the daily oral dose of each being 2.5 mg. per kg. of body weight. When toxic manifestations occur, azaserine may be discontinued for a few days and then restarted at half the dose. Many patients receiving combined treatment have shown no sign of toxicity when observed for as long as 10 months. The combination of these two drugs appears to delay the development of resistance to 6-MP and in addition increases the incidence of remissions over that achieved by 6-MP alone.

Early in 1957, DON was made available for use as an antileukemic agent. DON (6-diazo-5-oxo-*l*-norleucine) is an antibiotic isolated from Streptomyces and is similar in structure to its analogue, azaserine, but is approximately 50 times more potent by weight. Its mode of action as an anti-neoplastic agent is thought to be due to its interference with the enzyme system at the adenine level of protein synthesis. DON can be ad-

ministered by intravenous, intramuscular, subcutaneous and oral routes. The oral dosage is 0.25 mg. per kg. per day. Like azaserine, DON may cause oral ulcerations and gastrointestinal symptoms such as diarrhea, nausea and abdominal cramping. Cessation of therapy for two or three days usually results in disappearance of these toxic effects.

To date DON has been given to two of our patients with acute lymphocytic leukemia. It will be administered to alternate patients with this disease who are receiving 6-MP in an effort to evaluate its therapeutic potentialities. No conclusion concerning its effectiveness can be drawn at this early date.

Adrenal steroids. The use of adrenal steroid compounds is an important adjunct in the treatment of acute lymphocytic leukemia. The rapid effect obtained from the use of these drugs makes them particularly desirable in those patients with hemorrhagic manifestations, where the urgency of the situation does not allow enough time for the antimetabolites to act. The steroids supplement the action of the antimetabolites and are also employed when resistance to the antimetabolites has developed. Another important use is to achieve a maximum number of remissions. In order to obtain a more rapid response from the antimetabolite therapy used, some physicians prefer to use steroids at the onset of treatment.

Since the antimetabolites require from three to eight weeks to exert their maximal beneficial effects, the importance of prompt therapy with steroid compounds cannot be overemphasized, especially when serious bleeding threatens the life of the patient. Capillary hemorrhage tends to cease within four to five days after onset of steroid administration. The first hematological improvement seen is an increase in the number of the reticulocytes, and a rise in the hemoglobin and total red cell count, with an increase in the number of platelets in the peripheral blood. Clinically, the appetite of these patients begins to improve and they become active again. Remissions are attained more quickly and may last from 3 to 12 months. In our experience, however, remissions rarely exceed two and a half months and may not be complete.

Of the individual steroids, cortisone is given in divided doses of 25 to 150 mg. daily. The oral route is preferred as the danger of bleeding at the site of injection is thus eliminated. ACTH may also be employed, either intravenously or in the gel form intramuscularly. Prednisone (Meticorten®), however, has proven to be a more satisfactory compound, especially when the situation warrants the use of massive steroid therapy. The toxic dose usually has to be approached when there is impending bleeding as evidenced by thrombocytopenia or when another remission is desired. If remission is accomplished, the dosage is gradually reduced and supplemented with antimetabolites, such as 6-mercaptopurine or amethopterin, to prolong

the remission. During a relapse, the amount of steroid needed is usually greater than previously.

In order to minimize the electrolyte disturbances that may accompany the prolonged administration of steroids, adjunct therapy should be instituted when steroid therapy is begun. The low salt diet given to these children often introduces a problem for the parents. Potassium is given daily in an effort to prevent accumulation of excess sodium and minimize potassium deficiency. With the use of prednisone less sodium and fluid retention is noted.

Antibiotics. The increased susceptibility of these patients to infection is an important factor to be kept in mind while treatment is being carried out. Before the advent of the antibiotics, many patients died from fulminating infections. With the chemotherapeutic drugs available, many infections are cured or their severity lessened so that hospitalization can usually be curtailed, with some reduction in the cost of the treatment.

Therapeutic Approach

Transfusions both of whole blood and of packed cells are given in the beginning of the treatment and in periods of relapse, according to clinical judgment, whenever low hemoglobin levels or severe hemorrhagic manifestations require them.

Equally important is a rational approach by the physician to the patient and parents. An explanation of the nature of the illness should be imparted to them in order to secure their wholehearted cooperation. Although cure is not possible, they should be told that the overall survival time has been increased. The success of the treatment will depend mainly upon the understanding of the parents, the cooperation of the leukemic child, plus the early and judicious use of the various therapeutic agents by the physician.

SUMMARY

The average life span after diagnosis of patients with acute and chronic leukemia has been increased considerably in the past 10 years. The principle followed in Children's Hospital leukemia clinic is the administration either of one specific agent at a time or of a combination of synergistic agents. Azaserine when given with 6-mercaptopurine appears to be beneficial in some cases where the latter alone is no longer effective. Since, however, resistance ultimately follows the prolonged use of any antileukemic drug, the patient has to be given a sequential treatment either by adding another drug, by using the above combination of drugs, or by trying another available drug alone.

The adrenal steroids are valuable in the various stages of the disease.

They can be used to initiate treatment when there is danger of bleeding, and when a remission has to be quickly achieved. Once the desired effect of the drug has been obtained, the dose is gradually reduced and then discontinued, and one or more of the antimetabolites substituted.

In addition to the newer chemotherapeutic drugs, the antibiotics have played a major role in helping to prolong the lives of these patients by reducing the hazard of infection, formerly an important cause in precipitating the patient's death.

Lastly, the parents of the patient should have a good understanding of the course of the disease and the methods of treatment to be used; the physician should establish a sympathetic relationship with both the patient and the parents in order to achieve the maximum benefit from treatment through mutual cooperation.

ADDENDUM

Since the completion of this article, the patient referred to as having lived three and a half years after the diagnosis, expired, bringing his total life span to three years and eight months.

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ANOMALOUS PULMONARY VENOUS CONNECTION

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Recent advances in operative techniques for the repair of certain congenital heart anomalies have given hope that in the future more of the congenital cardiac lesions will be amenable to surgical correction. This particularly applies to the congenital cardiac defect known as anomalous pulmonary venous connection, a lesion for which not only a palliative procedure may be done but one which may be totally corrected. The following case report describes a death from anomalous pulmonary venous connection occurring in infancy, and the discussion following will describe latter day methods of diagnosis and operative repair.

CASE REPORT

This 4 month old white girl was admitted to Children's Hospital, April 18, 1957 because of dry cough, vomiting and cyanosis on crying.

The infant was born at term of a normal spontaneous delivery; her birth weight was 6 pounds 4 ounces. She had a normal growth and development, although her color was said to be "poor," and she had occasional colicky pains associated with constipation. At the age of 6 weeks her weight was 8 pounds and no abnormality was noted by her private physician. Since that time her weight gain was poor; a few days before admission she weighed only 9 pounds 1 ounce. About one month before admission it was noted that the baby had cyanosis of the face for a few seconds while crying. Later this cyanosis became more intense and lasted for several minutes. During the few days prior to admission the infant vomited almost all of her feedings and had a dry cough.

At the time of admission to the hospital the patient was a crying, poorly developed and poorly nourished infant. Her complexion was sallow, rectal temperature 98.8° F., respirations 40 to 50 per minute, pulse rate 160 to 180 per minute and weight 8 pounds 8 ounces. Blood pressure by flush technique was 80 mm Hg in the right arm, 50 mm Hg in the left, 66 mm Hg in the right leg and 66 mm Hg in the left. The face and nailbeds were moderately cyanotic. The precordial area of the chest was prominent and bulging slightly. The heart was enlarged to the left anterior axillary line and slightly to the right. An apical systolic thrill was palpable. A grade 3 apical systolic murmur was heard. The first heart sound at the apex was snapping and loud. Occasional rales were heard over the left chest. The liver was palpable 4 cm. below the right costal margin; the edge was firm and sharp. The femoral pulses were weak.

The patient was placed in an oxygen tent and an initial dose of Digalen 45 mg. was given; this was repeated in 12 hours. Antibiotic and supportive therapy was also started.

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From discussion at a monthly statistical conference.

The results of the x-ray examination of the chest were reported as follows: "Both lung fields are congested. There is a bulge in the left precordium and the heart is enlarged. The appearance is that of congenital heart disease with an increased pulmonary vascular flow. Congestive heart failure or bilateral bronchopneumonia cannot be excluded."

During the first days of hospitalization the patient took her feedings well but appeared cyanotic when fed or when out of oxygen. On the fourth hospital day she had a temperature of 104° F. and vomited her feedings. Her condition rapidly deteriorated and she died on the fifth hospital day.

Dr. Guin:

The significant pathologic findings in this infant were confined to the cardiovascular system. The heart was greatly enlarged, the enlargement being primarily right-sided. The superior vena cava was distended and engorged, and drained the pulmonary veins through a venous trunk which was situated in the left middle mediastinum. A branch of the anomalous vein reached the right lung by passing posterior to the aorta and pulmonary artery. The right auricle and ventricle were both markedly enlarged, and the pulmonary artery was also somewhat enlarged.

A review of statistics at this hospital brings to light that 20 to 25 per cent of deaths occurring each year are due to congenital heart disease. During the past 15 years, one or two patients every year have come to autopsy with a diagnosis of anomalous pulmonary venous connection.

Dr. Wedum:

Winslow[1], in 1739, was apparently the first person who ever observed an anomalous pulmonic venous connection. A number of sporadic case reports appeared in the medical literature down through the years until 1942 when Brody[2] summarized the cases which had been reported up to that time. Brody noted that there were about twice as many partial anomalies of the pulmonic venous connection as there were total anomalies of this defect. In 1954 Keith[3] collected a total of 58 cases from the literature.

The age of reported cases of total anomalous pulmonary venous return proven at autopsy at the time of diagnosis has ranged from 8 days to 31 years[4], (an additional probable case was aged 44)[5]. One case was found in a soldier, aged 24[6], who was completely asymptomatic. So, although 80 per cent die within the first year of life, anomalous pulmonary venous connection is not a lesion which is incompatible with life.

Embryologically, the pulmonic vein begins development at a fetal age of 23 days as an outgrowth from the left auricle, the so-called caudal evagination. It establishes connection with the lung buds and ultimately the common pulmonary vein is absorbed into the left auricle so that four venous orifices into the left auricle remain[7]. There are various ways in which this development may go astray. The pulmonary veins may drain

indirectly into a persistent left superior vena cava. They may also connect directly with the right auricle or veins of the splanchnic system. Uncommon sites of drainage include the ductus venosus, azygos vein, and inferior vena cava.

The most common form that this anomaly may take is drainage into the right auricle by way of a persistent common pulmonary vein. This is called the left superior vena cava. Actually, it is not a left superior vena cava, but this term persists in the literature.

In the patient with total anomalous pulmonary venous connection there is massive enlargement of the right side of the heart due to the fact that all pulmonary veins drain into the right auricle. The blood can only reach the left side of the heart through an auricular septal defect. The left side of the heart through which little blood has passed during fetal life is very small. Consequently it is impossible to repair these lesions at one stage by anastomosing the common pulmonary vein to the left auricle and closing the auricular septal defect simultaneously, since the left auricle cannot accomodate the sudden increased pulmonary venous return. It is necessary first to create the anastomosis to the left auricle with varying degrees of occlusion of the entrance of the common pulmonary vein to the right auricle, depending on the size of the auricular septal defect. Later, when the left auricle has grown, the auricular septal defect may be closed. The anastomosis must be made to the waist of the left auricle, not to the appendage, since the junction of the appendage with the auricle may be very small.

Clinically this condition is not too difficult to diagnose. These infants usually have a history of repeated respiratory infections. Cyanosis is usually minimal and is of the type one sees with diminished cardiac output; it is not the typical cyanosis of frank right to left shunt. All peripheral pulses are weak since only a small amount of blood is reaching the peripheral circulation. About 75 per cent of cases have a systolic murmur, and may have a venous hum which may sound very much like a patent ductus arteriosus. There is early evidence of congestive heart failure.

Electrocardiographically, the P wave is of variable height but may be quite high if the auricular septal defect is small. Depending on one's imagination, roentgenograms may show the typical "figure of eight," "mediastinal snowman," or "cottage loaf"[8] type of configuration of the cardiac shadow. The typical cardiac contour is due to the bulge of the common pulmonary vein draining into the right auricle. Unfortunately, infants do not always have this typical finding. There is also marked congestion of the lung fields. In the differential diagnosis of total anomalous pulmonary venous connection, four lesions primarily must be considered. The first is transposition of the great vessels. Infants with this condition are usually

deeply cyanotic and have *normal* peripheral pulses. The presence of reduced peripheral pulses practically eliminates the possibility of a transposition. The radiographic contour is, of course, not the same since the right auricle is much larger in anomalous pulmonary venous connection. Another congenital cardiac lesion which must be considered in the differential diagnosis is transposition with a single ventricle which may be ruled out largely on the basis of differences in radiographic contour and the electrocardiogram. Complete aortic atresia very closely resembles total anomalous pulmonary venous connection. Both lesions have right ventricular preponderance, congested lung fields and weak peripheral pulses. Infants with aortic atresia, however, get into trouble much earlier, and from a practical standpoint are inoperable and therefore die at an early age. The most important lesion to be considered in the differential diagnosis is preductal coarctation of the aorta. Good flush technique blood pressure determinations confirm the diagnosis of this condition. However, when the infant does not have much cyanosis, has diminished peripheral pulses and an electrocardiogram which demonstrates marked right ventricular preponderance with congestion of the lung fields, anomalous pulmonary venous connection should be the first lesion to be considered, first, because it is not uncommon, and second, because it can be totally repaired. Six cases of this anomaly have come to autopsy at Children's Hospital since January 1953.

The first successful repair was done by Dr. William Muller of Charlottesville, Virginia[9]. Recently Dr. William Mustard of Toronto [10] has reported 9 cases operated on under hypothermia ranging in age from 3 months to 5 years, 4 of which survived including the youngest case. Dr. Muller at present is considering closing the auricular septal defect with a perforated plastic material at the time the anastomosis of the common pulmonary vein to the left auricle is made, in hopes that the auricular septal defect will completely endothelialize as the left side of the heart enlarges to accommodate the pulmonary venous return[11]. In this way a two stage procedure could be avoided.

Dr. Hufnagel:

The most common of the venous anomalies is probably persistence of the left superior vena cava. This ordinarily courses down the left side and passes behind the heart in the region of the coronary sinus. At surgery one may be confused by this large vessel which appears to be in the left side of the heart until he traces it a little farther and finds that it really enters the right atrium. Anomalies of pulmonary venous drainage are most commonly partial and associated with an interatrial septal defect. However, there are many variations of this.

In cardiac catheterization, especially, it is difficult to decide whether

the pulmonary venous connection is truly anomalous in the presence of an interatrial septal defect or whether one is merely getting a shunt of blood across a large septal defect alone. This is easy to understand when one explores the inside of the heart and finds that the remnant of the interatrial septum is located relatively posterior and the veins are actually entering to the left of the septum. The septum in these cases is frequently a tiny rim of one or two millimeters in height, and as the catheter is passed into the right atrium it can receive blood from one of these anomalously returning pulmonary veins, or accidentally pass through an interatrial septal defect into the left side and into a normally located pulmonary vein. Since this catheter manipulation involves only a few millimeters it might be quite difficult to determine which of the two anomalies is present.

Early in the experience with this lesion a great deal of difficulty was experienced when an attempt was made at total correction in a single stage. More recently it has become customary in the first stage of a two stage procedure to attempt only to redirect the venous drainage back into the left side. This may be done in a number of ways, the most common probably being a direct anastomosis to the left auricle with or without a short graft. The other defects are allowed to persist with the idea that they could be corrected at a later time. If there is also an interatrial septal defect, unless this is closed, the patient will still have all the problems associated with this anomaly alone as time goes on. Closure of an interatrial septal defect either under direct vision or by any one of a number of standard indirect methods is associated with a relatively low mortality rate. Operative difficulty is greatly increased the longer the situation is allowed to persist. If the patient is in the terminal phase of his disease and has extreme pulmonary hypertension, the problems associated with surgery are multiplied, whereas if operative intervention can be performed when pulmonary hypertension is moderate, patients may have very little difficulty. Between the ages of 4 and 12 years a child may rapidly pass from a phase in which he is relatively asymptomatic into profound congestive heart failure.

The correction of partial transposition of the veins or partial anomalous venous drainage can in general be handled quite satisfactorily. A single anomalous vein entering the superior vena cava from the right side can either be transposed into one of the veins entering the left side of the heart or directly anastomosed into the left atrium. When anomalous drainage exists in association with a large interatrial septal defect, and this anomalous drainage is from the right lung alone, one can usually re-position the septum in such a location that the drainage then all enters the left atrium.

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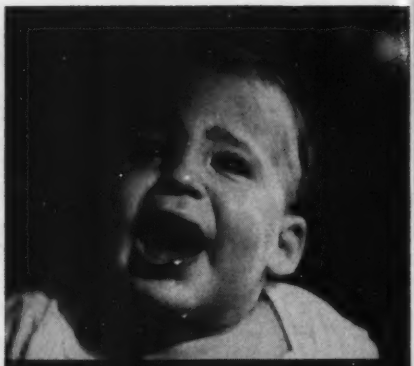

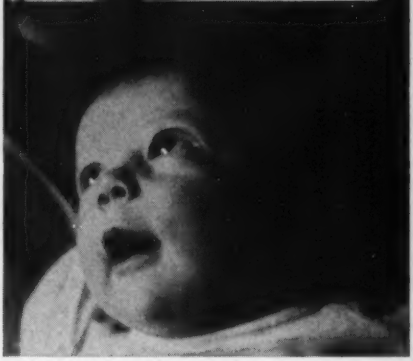

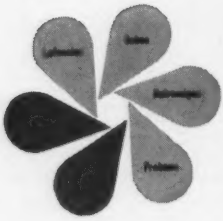

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